C. Remarks

The claims are 1-20, with claim 1 being the sole independent claim. Claim 3 has been amended to correct an informality; no new matter has been added. Reconsideration of the claims is respectfully requested in light of the following remarks.

Applicant notes with appreciation the Examiner's indication that claims 10-13 and 15 are directed to allowable subject matter.

Claim 3 stands rejected under 35 U.S.C. §112, second paragraph. In light of Applicant's amendment of claim 3 to address the Examiner's concern with regard to antecedent basis, Applicant submits that the rejection is now moot and should be withdrawn.

Claims 1, 2, 4-9, 14 and 16-20 stand rejected under 35 U.S.C. §103(a) as being obvious over Burger ("Regiospecific Reactions with ω-carboxy-α-amino acids -- A Simple Synthesis of Aspartame", *Chemmiker Zeitlung*, 1990, 114(7-8), pp. 249-251) and further in view of Claude (U.S. Patent No. 5,510,508). Applicant respectfully traverses this rejection.

All of the arguments advanced in previous responses are incorporated by reference herein. Instead of presenting said arguments again in this paper, Applicant would like to directly address the Examiner's rebuttal to those previously advanced arguments as set forth in the outstanding Office Action. The first of the Examiner's contentions with which Applicant takes issue is:

> There is no evidence in the prosecution history of this application that supports the assertion that aldehydes can be used in the synthesis of aspartame via a process analogous to that taught by Burger. Burger teaches only the use of hexafluoroacetone as a carbonyl component. Applicant has not provided any evidence to support the assertion that aldehydes may be used to replace the ketone taught by Burger. Office Action, page 5, lines 12-17.

Applicant respectfully disagrees with the Examiner's position. In fact, Chinese Patent Application No. 1174844 (cited in the present specification and also in the Information Disclosure Statement of November 2, 2001) contains such evidence of the successful use of aldehydes in the synthesis of aspartame via a process analogous to that taught by Burger. A partial translation of CN 1174844 is attached to this response paper; both examples 1 and 2 evidence the success in using Cl_3CCHO (an aldehyde) to first synthesize an oxazolidinone derivative and to ultimately synthesize aspartame. Accordingly, the Examiner's first contention cannot be maintained.

Second, Applicant takes issue with the following contention advanced by the Examiner:

> Because the prior art of record teaches only the use of ketones, the differences in behavior with aldehydes of the starting materials for the synthesis of aspartame and neotame does not appear to be particularly relevant in this context. The starting materials for the synthesis of aspartame and neotame are different compounds, having different chemical structures, and are thus expected to exhibit different chemical behaviors. Those differences would not, however, prevent a reasonable expectation of success in the application of the process of Burger to the synthesis of neotame. Office Action, page 5, line 18, through page 6, line 4.

Applicant respectfully and completely disagrees with the Examiner's position that the information regarding the success in using aldehydes in the oxazolidinone-intermediated synthesis of aspartame is irrelevant. The Examiner has taken the position that because of the structural similarity between the two starting materials, i.e., neohexyl aspartic acid (N-(3,3-dimethylbutyl)-L-aspartic acid) and aspartic acid (L-aspartic acid), one of ordinary skill in this art would certainly have had a reasonable expectation of success in using the two starting materials in similar syntheses with similar results.

Applicant fundamentally disagrees with the Examiner and has consistently argued the reverse: no assumptions can fairly be made regarding the behavior of neotame based on the behavior of aspartame or regarding the behavior of neohexyl aspartic acid based on the behavior of aspartic acid; no reasonable expectation of success can be had with regard to neotame (or its starting material) based on a behavior of aspartame (or its starting material). One of ordinary skill in this art would know such statements to be true based on the physical, chemical and structural differences between neotame and aspartame and between neohexyl aspartic acid and aspartic acid. These statements are evidenced by Dr. Prakash's April 28, 2003, declaration, and, to counter the Examiner's second contention, these statements are now further evidenced by the lack of interchangeability between neohexyl aspartic acid and aspartic acid when synthesizing neotame and aspartame, respectively, via oxazolidinone intermediates. Therein lies the relevance of the success in using aldehydes in the oxazolidinone-intermediated synthesis of aspartame.

The success in using aldehydes in the oxazolidinone-intermediated synthesis of aspartame confirms Applicant's consistent belief that no reasonable expectation of success existed with regard to the present invention. The success in using aldehydes in the oxazolidinone-intermediated synthesis of aspartame is concrete evidence that the presence of the neohexyl group on neohexyl aspartic acid does affect the reaction, that the neohexyl group is more that just a "spectator" as the Examiner maintains in his third contention:

> Applicant's general statements to the effect that the starting compounds have different properties do not shed light on why one of ordinary skill in the art would have not had a reasonable expectation of success. All the required features (shown in bold above) for reaction are present. The additional substitution found on the nitrogen atom in the starting material for the synthesis of neotame (INVENTION) is simply a spectator and does not participate in any direct fashion in the process. Since all the required atoms are present in the proper arrangement, one of ordinary skill in the art

would have had a reasonable expectation of success. Office Action, page 6, lines 7-16.

The Examiner's present position is basically this: because there is such a simple structural difference between neohexyl aspartic acid and aspartic acid and because all of the atoms necessary to the reaction scheme are in the proper arrangement, then a reasonable expectation of success existed. Applicant's argument has consistently been this: even a simple structural difference can have profound effects, and the simple difference between neohexyl aspartic acid and aspartic acid prevent a reasonable expectation of success in the present invention. Both Applicant and anyone of ordinary skill in this art would readily recognize the potential impact that a neohexyl group can have upon any reaction scheme. Systems containing bulky, electron-donating neohexyl groups are subject to severe steric hindrance and have been known to experience unwanted rearrangements.

The Examiner's position that the neohexyl group is "simply a spectator" is not true in all reaction schemes. In fact, it is not true when neohexyl aspartic acid is reacted with an aldehyde in an attempt to synthesize an oxazolidinone and ultimately neotame. If the neohexyl group were only a spectator, then the oxazolidinone-intermediated synthesis of neotame would work when using an aldehyde starting material, as such a synthesis does work with respect to aspartame; however, such a neotame synthesis does not work. Why the neohexyl group does not interfere in the oxazolidinone-intermediated synthesis of neotame using a ketone starting material is not clear. However, it is this very unpredictability of a neohexyl group in any given reaction scheme that is the basis for a lack of reasonable expectation of success in the present invention.

In sum, Applicant earnestly submits that the Examiner's contentions have been countered and that the present invention is not obvious in light of the cited art. Applicant respectfully requests withdrawal of the §103 rejection.

In view of the foregoing amendments and remarks, favorable reconsideration and passage to issue of the present case is respectfully requested. Should the Examiner believe that issues remain outstanding, the Examiner is respectfully requested to contact Applicant's undersigned attorney in an effort to resolve such issues and advance the case to issue.

Applicant's undersigned attorney may be reached in our New York office by telephone at (212) 218-2100. All correspondence should continue to be directed to our below listed address.

Respectfully submitted,

Attorney for Applicant

Registration No. 42,667

FITZPATRICK, CELLA, HARPER & SCINTO
30 Rockefeller Plaza
New York, New York 10112-3801
Facsimile: (212) 218-2200

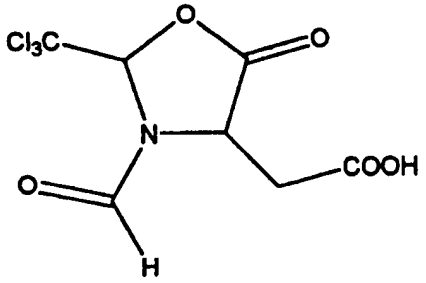
NY_MAIN 367303v1

Translated CHINESE PATENT APPLICATION 3-3-03

SEP 0 5 2003 TRADEMARK OFFICE

Example 1

To a 250 ml round bottom flask was added 13.4 g (0.1 mole) L-aspartic acid, 11 ml (0.248 mole) 85% formic acid and 60 ml acetic anhydride (0.64 mole). The mixture was stirred at room temperature for 15 minutes followed by addition of 19.5 ml (0.2 mole) Cl_3CCHO and 100 ml acetic acid. The mixture was stirred and heated at 75 C for 15 hours to yield a light yellow solution. The solvents were removed at < 50 C with vacuum. The oily residue was dissolved in 30 ml dichloromethane and the solution was cooled to -10 C for crystallization. The crystals were isolated, washed with pet ether and dried. Yield Compound A 20 5 g (70.6%). M.p. 125-127 (dec.).



A

To a 100 ml 3-necked flask was loaded 11.62 g (0.04 mole) A and 40 ml THF. 7.16 g (0.04 mole) L-Phe-Me was added drop-wise at RT. After the addition, the mixture was stirred at 40 C for 12 hours. After vacuo removal of solvents, the residue was treated with 20 ml water and dilute NaOH solution until pH 9. Washed with 2x20 ml diethyl ether. The water layer was ajusted to pH 2-3 with dilute hydrochloric acid. Cooled, filtered to isolated the APM solid, which is washed with ice-water and dried. Yield: 9.92 g (77%). M.p. 132-135 C.

6.44 g (0.02 mole) the above APM was dissolved in 2 ml MeOH followed by addition of 1.8 ml concentrated hydrocloric acid. Cooled to -10 C for crystallization. Filtered and isolated the solid APM HCl salt, which is dissolved in 4 ml water and adjusted to pH 4.8 with sodium bicarbonate to precipitate the solid. The solid was isolated and dried to give APM 4.41 g (75% yield). M.p. 240-243 C.

Example 2

8.62 g (0.04 ml) L-Phe-Me.HCl , 40 ml THF and 3.28 g (0.04 mole) NaOAc were loaded to a 100 ml flask.n The mixture was stirred at RT for 15 minutes and to which was added 11.62 (0.004 mole) A synthesized according to Example 1. Stirred at 25 C for 23 hours. Worked up using a procedure similar to Example 1 to yield APM 10.26 g (79.7 %).

[19]中华人民共和国专利局

[51]Int.Cl[6]
C07K 5/06
C07K 1/02

[12] 发明专利申请公开说明书

[21] 申请号 96117685.7

[43]公开日 1998 年 3 月 4 日

[11] 公开号 CN 1174844A

[22]申请日 96.8.28
[71]申请人 中国科学院成都有机化学研究所
地址 610041四川省成都市人民南路四段九号
[72]发明人 杨桂树 李 艳 陈志勇
岳智洲 宓爱巧 蒋耀忠

[74]专利代理机构 中国科学院成都专利事务所
代理人 杨俊华

权利要求书 1 页 说明书 13 页 附图页数 0 页

[54]发明名称 N-保护天冬甜肽的制备方法

[57]摘要

本发明是N（N代表氨基，以下同）-保护天冬甜肽的制备方法，从L-天冬氨酸出发，一步合成N-保护的吡唑烷酮，在接肽反应中使用醋酸酯等低毒或无毒溶剂，该方法无β-异构体生成，合成路线短，生产成本低，反应产率高，有利于工业化生产。

权 利 要 求 书

1、一种N(N代表氨基，以下同)-保护的天冬甜肽的制备方法，其特征在于以L-天冬氨酸、酰化剂、活性羰基化合物为原料，在醋酸酐、醋酸的存在下，进行噁唑烷酮化反应，一步合成2-取代-3-N-酰基化-5-氧-4-噁唑烷乙酸，将此产物再于低毒或无毒的极性溶剂中与L-苯丙氨酸甲酯或其盐、碱进行接肽反应，制得N-保护的天冬甜肽，其中：

a、噁唑烷酮化反应中，酰化剂为甲酸、醋酸酐，活性羰基化合物为三氯乙醛、三溴乙醛、六氯丙酮、六氟丙酮，其用量比为：天冬氨酸(摩尔)：酰化剂(摩尔)：活性羰基化合物(摩尔)：醋酸酐(摩尔)：醋酸(升)= 1:1.2～4.0:1.2～4.0:2.5～10.0:0.5～2.0，反应温度为30℃～100℃，反应时间为6～30小时

b、接肽反应中溶剂为醋酸酯、乙醚、四氢呋喃、二氧六环，用量比为L-苯丙氨酸甲酯(摩尔)：2-取代-3-N-酰基化-5-氧-4-噁唑烷乙酸(摩尔)：溶剂(升)= 1:1～1.5:0.5～3，或L-苯丙氨酸甲酯盐(摩尔)：碱(摩尔)：2-取代-3-N-酰基化-5-氧-4-噁唑烷乙酸(摩尔)：溶剂(升)= 1:1～1.5:1～1.3:0.5～3 反应温度为20℃～100℃，反应时间为4～30小时

2、根据权利要求1所述的N-保护的天冬甜肽的制备方法，其特征在于接肽反应中的L-苯丙氨酸甲酯盐为盐酸盐、硫酸盐，碱为碱金属或碱土金属的有机酸盐，叔胺，如醋酸盐，三乙胺。

3、根据权利要求1所述的N-保护的天冬甜肽的制备方法，其特征在于噁唑烷酮化反应时的最佳温度为50℃～85℃。

4、根据权利要求1所述的N-保护的天冬甜肽的制备方法，其特征在于甲酸的浓度可用80%～98%

5、根据权利要求1所述的N-保护的天冬甜肽的制备方法，其特征在于噁唑烷酮化反应时噁唑烷酮的析出试剂为卤代烷烃。

说　明　书

氨基-保护天冬甜肽的制备方法

本发明是N(N代表氨基，以下同)-保护天冬甜肽的制备方法，涉及多肽的合成方法，特别是关于二肽甜味剂的合成方法。

天冬甜肽(α-L-天冬氨酰-L-苯丙氨酸甲酯)是一种具有蔗糖甜度200倍的天然型二肽甜味剂，具有甜度高、热值低、口感佳、无毒副作用等优点，广泛的应用于食品、饮料领域。

自从1969年Muzar有关该二肽合成的第一篇文献报道(J. Am. Chem. Soc,1969;91:2684)以来，已经有大量的文献报道其合成。一类是酸酐法，将L-天冬氨酸制成N-保护的天冬氨酸酐，再与L-苯丙氨酸甲酯进行接肽反应，制成N-保护的天冬甜肽，然后脱除保护基而得天冬甜肽。如US 5,334,746；US 4,684,745；JP 56-75,053；EP 221，878等。其中的美国专利具有路线短的优点，但收率低，有β-异构体的产生，增加了分离、回收工序，不利于工业化生产；日本专利利用硫代羰基进行N-保护，虽然无β-异构体，但合成的天冬甜肽因含硫而具有不愉快的异味。欧洲专利用羰基进行N-保护，也无β-异构体，但因制备N-保护的天冬酸酐时需用剧毒的光气而限制了工业化生产。另一类是噁唑烷酮法，将L-天冬氨酸进行N-保护后，与醛类化合物反应制成噁唑烷酮，再经接肽反应，脱保护基而得天冬甜肽。如JP 87-164,692；JP 91-255,093。此法具有高选择性和高产率，但接肽反应是用苯、二氯甲烷等有毒溶剂，对环保和工人健康都不利，接肽产物用Pd/C还原，增加了生产成本。还有许多关于接肽中间体天冬氨酸的噁唑烷酮的研究，如Ber 95,1009-15；Khim. Geterotsikl Soedin 1978,(11) 1472-3；Synthesis 1989,542等。但这些研究存在以下缺点：1、将天

冬氨酸经N-保护后再与醛类化合物反应制备噁唑烷酮，这种两步法使步骤及辅助试剂增多，因而总收率降低，生产成本增加；2.保护基试剂价格昂贵，不易脱保护；3.接肽产物中N-羟甲基在酸性条件下不易水解脱去，

本发明的目的在于提供一种无β-异构体生成的区域选择性合成N-保护的天冬甜肽的制备方法，从L-天冬氨酸出发一步合成N-保护的噁唑烷酮，形成肽键的反应中使用低毒或无毒溶剂，并同时脱去保护基，产物收率高，生产成本低。

本发明的目的是这样实现的：以L-天冬氨酸、酰化剂、活性羰基化合物为原料，在醋酸酐、醋酸存在下，进行噁唑烷酮化反应，一步合成2-取代-3-N-酰基化-5-氧-4-噁唑烷乙酸，将此产物在低毒或无毒的极性溶剂中与L-苯丙氨酸甲酯或其盐、碱进行接肽反应，制得N-保护的天冬甜肽，其中：a、噁唑烷酮化反应中，酰化剂为甲酸或醋酸酐，活性羰基化合物为三氯乙醛、三溴乙醛、六氟丙酮、六氟丙酮，其用量比为：L-天冬氨酸(摩尔)：酰化剂(摩尔)：活性羰基化合物(摩尔)：醋酸酐(摩尔)：醋酸(升)＝1:1.2∽4.0:1.2∽4.0:2.5∽10.0:0.5∽2.0，反应温度为30℃∽100℃，反应时间为6∽30小时；b、接肽反应中溶剂为醋酸酯、乙醚、四氢呋喃、二氧六环，用量比为L-苯丙氨酸甲酯(摩尔)：2-取代-3-N-酰基化-5-氧-4-噁唑烷乙酸(摩尔)：溶剂(升)＝1:1∽1.5:0.5∽3，或L-苯丙氨酸甲酯盐(摩尔)：碱(摩尔)：2-取代-3-N-酰基化-5-氧-4-噁唑烷乙酸(摩尔)：溶剂(升)＝1:1∽1.5:1∽1.3:0.5∽3。反应温度为20℃∽100℃，反应时间为4∽30小时。

其中的酰化剂用甲酸时产物N-保护基为甲酰基，可以直接使用

的甲酸浓度为80％-98％。用醋酸酐时产物N-保护基为乙酰基。活性羰基化合物用于与天冬氨酸的氨基和α-羧基形成五元杂环化合物—噁唑烷酮，并决定2-取代基的种类。醋酸酐用于脱除甲酸中水份和反应过程中产生的水，同时将甲酸转化成甲酸乙酸酐，后者是更有效的甲酰化试剂；在进行乙酰化时，则直接作为酰化剂。

醋酸作为溶剂，同时还起催化作用。反应结束后醋酸可回收再利用。

L-苯丙氨酸甲酯盐为盐酸盐、硫酸盐。

碱为碱金属或碱土金属的有机酸盐、叔胺，如醋酸盐、三乙胺等。

噁唑烷酮化反应时的最佳温度为50℃～85℃。

本发明的具体操作为将L-天冬氨酸、酰化剂、活性羰基化合物、醋酸酐、醋酸按配比在搅拌下进行噁唑烷酮化反应，反应结束后除去醋酸，加入卤代烷烃溶解，冷冻结晶，过滤，洗涤，干燥得噁唑烷酮产物，将此产物与接肽溶剂、L-苯丙氨酸甲酯或其盐按配比在搅拌下进行接肽反应，反应结束后，除去溶剂，加水洗涤，干燥得N-保护的天冬甜肽。

本发明所制备的N-保护的天冬甜肽在醇、盐酸、水的混合溶液中很容易脱去保护基而得天冬甜肽。

本发明是将现有技术中的两步法并为一步制备噁唑烷酮，区域选择性合成N-保护的天冬甜肽，无β-异构体生成，合成路线短，反应产率高，所用溶剂低毒或无毒，生产成本低，有利于工业化生产。

下面是本发明的实施例：

实施例一

在250毫升圆底烧瓶中加入13.4克(0.1摩尔)L-天冬氨酸，11毫升(0.248摩尔)85%甲酸和60毫升(0.64摩尔)乙酸酐，室温搅拌15分钟后，加入19.5毫升(0.2摩尔)三氯乙醛和100毫升乙酸，油浴加热，升温至75℃，反应15小时得一淡黄色澄明液，50℃以下减压除去溶剂，得一棕色油状液．加入30毫升二氯甲烷溶解，-10℃冷冻，析出晶体，过滤，石油醚洗涤，干燥得白色的2-三氯甲基-3-N-甲酰基-5-氧-4-噁唑烷乙酸20.5克，产率:70.6%；MP:125～127℃(分解)。

在100毫升三颈瓶中加入上述的噁唑烷酮11.62克(0.04摩尔)和40毫升四氢呋喃，机械搅拌下，室温滴加7.16克(0.04摩尔)L-苯丙氨酸甲酯，滴加完毕，40℃恒温反应12小时，减压除去溶剂，残渣加水20毫升，稀氢氧化钠溶液中和至PH9，乙醚20毫升×2洗涤，水层用稀盐酸中和至PH2-3，冷冻，过滤，冰水洗涤，干燥得白色的N-甲酰基-天冬甜肽9.92克，产率：77.0%；MP：132～135℃。

在2毫升甲醇、3.5毫升水和1.8毫升37%盐酸的混合溶剂中，加入上述的N-甲酰基-天冬甜肽6.44克(0.02摩尔)，于55℃反应1小时，-10℃下冷却析出晶体，过滤，得天冬甜肽盐酸盐，将此盐酸盐溶于4毫升水，用碳酸钠调PH值为4.8，析出固体，过滤，干燥，得天冬甜肽4.41克，产率75%，MP：240～243℃，$[\alpha]_D^{20}=15.0$ (4%，甲酸)。

实施例二

在100毫升三颈瓶中加入8.62克(0.04摩尔)L-苯丙氨酸甲酯盐酸盐、40毫升四氢呋喃和3.28克(0.04摩尔)醋酸钠，室温机械搅拌15分钟后，加入11.62克(0.04摩尔)按实施例一制的噁唑烷酮，25℃恒温反应23小时，反应条件、操作按实施例一得N-甲酰基-天冬甜肽10.26克，产率：79.7%。

实施例三

在250毫升圆底烧瓶中加入13.4克(0.1摩尔)L-天冬氨酸，7毫升(0.158摩尔)85%甲酸和40毫升(0.42摩尔)乙酸酐，室温搅拌15分钟后，加入19.5毫升(0.2摩尔)三氯乙醛和60毫升乙酸，油浴加热，升温至60℃，反应24小时，反应条件、操作按实施例一得2-三氯甲基-3-N- 甲酰基-5- 氧-4- 噁唑烷乙酸16.0克，产率：55.1%。

在100毫升三颈瓶中加入40毫升乙酸乙酯和5.81克(0.02摩尔)上述的噁唑烷酮化合物，机械搅拌下，室温滴加3.58克(0.02摩尔)L-苯丙氨酸甲酯，滴加完毕，25℃恒温反应23小时，直接过滤，冰水洗涤，得N-甲酰基-天冬甜肽4.60克，产率：71.4%。

实施例四

在100毫升三颈瓶中加入60毫升乙酸乙酯、12.93克(0.06摩尔)L-苯丙氨酸甲酯盐酸盐和4.92克(0.06摩尔)醋酸钠，室温机械搅拌15分钟，加入17.45克(0.06摩尔)按实施例三制备的噁唑烷酮化合物，60℃恒温反应7小时，反应条件、操作按实施例三得N-甲

酰基-天冬甜肽14.3克，产率：74.0%。

实施例五

在250毫升圆底烧瓶中加入13.4克（0.1摩尔）L-天冬氨酸，8.5毫升（0.198摩尔）88%甲酸和50毫升（0.53摩尔）乙酸酐，室温搅拌15分钟后，加入19.5毫升（0.2摩尔）三氯乙醛和100毫升乙酸，油浴加热，升温至75℃，反应15小时反应条件、操作按实施例一得2-三氯甲基-3-N-甲酰基-5-氧-4-噁唑烷乙酸18.9克，产率：65.1%。

在100毫升三颈瓶中加入上述的噁唑烷酮6.4克（0.022摩尔）和40毫升乙酸丁酯，机械搅拌下，室温滴加3.58克（0.02摩尔）L-苯丙氨酸甲酯，滴加完毕，40℃恒温反应12小时，反应条件、操作按实施例一得N-甲酰基-天冬甜肽5.28克，产率：82.0%。

实施例六

在100毫升三颈瓶中加入30毫升乙酸丁酯、4.31克（0.02摩尔）L-苯丙氨酸甲酯盐酸盐和1.64克（0.02摩尔）醋酸钠，室温机械搅拌15分钟，加入8.12克（0.028摩尔）按实施例五制备噁唑烷酮化合物，25℃恒温反应24小时，反应条件、操作按实施例一得N-甲酰基-天冬甜肽5.51克，产率：85.5%。

实施例七

在500毫升圆底烧瓶中加入13.4克（0.1摩尔）L-天冬氨酸，11毫升（0.255摩尔）88%甲酸和80毫升（0.85摩尔）乙酸酐，室温搅拌

15分钟后，加入24.5毫升(0.25摩尔)三氯乙醛和150毫升乙酸，油浴加热，升温至85℃．反应10小时，反应条件、操作按实施例一得2-三氯甲基-3-N-甲酰基-5-氧-4-噁唑烷乙酸21.8克，产率：75.0%。

在100毫升三颈瓶中加入40毫升乙酸乙酯、4.31克(0.02摩尔)L-苯丙氨酸甲酯盐酸盐和1.64克(0.02摩尔)醋酸钠，室温机械搅拌15分钟，加入6.39克(0.022摩尔)上述的噁唑烷酮化合物，40℃恒温反应12小时，反应条件、操作按实施例一得N-甲酰基-天冬甜肽5.06克，产率：78.6%

实施例八

在100毫升三颈瓶中加入30毫升乙酸乙酯、4.31克(0.02摩尔)L-苯丙氨酸甲酯盐酸盐和1.64克(0.02摩尔)醋酸钠，室温机械搅拌15分钟，加入6.97克(0.024摩尔)按实施例七制备的噁唑烷酮化合物，60℃恒温反应7小时．反应条件、操作按实施例三得N-甲酰基-天冬甜肽5.32克，产率：82.6%。

实施例九

在250毫升圆底烧瓶中加入13.4克(0.1摩尔)L-天冬氨酸，13.3毫升(0.30摩尔)85%甲酸和50毫升(0.53摩尔)乙酸酐，室温搅拌15分钟后，加入14.7毫升(0.15摩尔)三氯乙醛和100毫升乙酸，油浴加热，升温至80℃，搅拌12小时得一淡黄色澄明液，低于50℃减压除去溶剂，得一棕色油状液，加入30毫升1,2-二氯乙烷溶解，-10℃冷冻，析出晶体，过滤，石油醚洗涤，干燥，得白色的2

-三氯甲基-3-N-甲酰基-5-氧-4-噁唑烷乙酸 14.8克，产率：50.8%。

在100毫升三颈瓶中加入30毫升乙酸丁酯、4.31克(0.02摩尔)L-苯丙氨酸甲酯盐酸盐和2.02克(0.02摩尔)三乙胺，室温机械搅拌15分钟，加入5.82克(0.02摩尔)上述的噁唑烷酮化合物，60℃恒温反应8小时，反应条件、操作按实施例三得N-甲酰基-天冬甜肽4.86克，产率：75.5%

实施例十

在100毫升三颈瓶中加入30毫升乙酸乙酯、4.31克(0.02摩尔)L-苯丙氨酸甲酯盐酸盐和2.85克(0.02摩尔)醋酸镁，室温机械搅拌15分钟，加入5.82克(0.02摩尔)按实施例九制备的噁唑烷酮化合物，40℃恒温反应10小时，反应条件、操作按实施例一得N-甲酰基-天冬甜肽3.56克，产率：55.2%。

实施例十一

在500毫升圆底烧瓶中加入13.4克(0.1摩尔)L-天冬氨酸，50毫升(0.53摩尔)乙酸酐和150毫升乙酸，室温搅拌15分钟后，加入24.5毫升(0.25摩尔)三氯乙醛，油浴加热，60℃反应15小时，反应条件、操作按实施例九得2-三氯甲基-3-N-乙酰基-5-氧-4-噁唑烷乙酸19.6克，MP：130～133℃，产率：64.4%。

在100毫升三颈瓶中加入30毫升乙酸丁酯、4.31克(0.02摩尔)L-苯丙氨酸甲酯盐酸盐和1.62克(0.02摩尔)醋酸钠，室温机械搅拌15分钟，加入6.1克(0.02摩尔)上述的噁唑烷酮化合物，40℃

恒温反应12小时，反应条件、操作按实施例三得N-乙酰基-天冬甜肽4.46克，产率：66.4%，MP：140～142℃。

实施例十二

在250毫升圆底烧瓶中加入13.4克(0.1摩尔)L-天冬氨酸，30毫升(0.32摩尔)乙酸酐和50毫升乙酸，室温搅拌15分钟后，加入17.5毫升(0.18摩尔)三氯乙醛，油浴加热，85℃反应10小时，反应条件、操作按实施例一得2-三氯甲基-3-N-乙酰基-5-氧-4-噁唑烷乙酸16.0克，产率：52.4%

在100毫升三颈瓶中加入30毫升乙酸乙酯、4.31克(0.02摩尔)L-苯丙氨酸甲酯盐酸盐和1.64克(0.02摩尔)醋酸钠，室温机械搅拌15分钟，加入6.1克(0.02摩尔)上述的噁唑烷酮化合物，60℃恒温反应8小时，反应条件、操作按实施例三得N- 乙酰基- 天冬甜肽4.85克，产率：72.2%。

实施例十三

在250毫升圆底烧瓶中加入13.4克(0.1摩尔)L-天冬氨酸，16毫升(0.37摩尔)88% 甲酸和70毫升(0.74摩尔)乙酸酐，室温搅拌15分钟后，加入53克(0.2摩尔)六氯丙酮和100毫升乙酸，油浴加热，升温至50℃，反应15小时．反应条件、操作按实施例一得2,2-二-三氯甲基-3-N-甲酰基-5-氧-4-噁唑烷乙酸14.8克，产率：36.3%。

在100毫升三颈瓶中加入30毫升乙酸丁酯、4.31克(0.02摩尔)L-苯丙氨酸甲酯盐酸盐和1.64克(0.02摩尔)醋酸钠，室温机械

搅拌15分钟，加入8.12克(0.02摩尔)上述的噁唑烷酮化合物，60℃恒温反应8小时，反应条件、操作按实施例三得N-甲酰基-天冬甜肽4.68克，产率：72.7%。

实施例十四

在250毫升圆底烧瓶中加入13.4克(0.1摩尔)L-天冬氨酸，11毫升(0.255摩尔)88%甲酸和50毫升(0.53摩尔)乙酸酐，室温搅拌15分钟后，加入66.3克(0.25摩尔)六氯丙酮和120毫升乙酸，油浴加热，升温至90℃反应8小时，反应条件、操作按实施例九得2,2-二-三氯甲基-3-N-甲酰基-5-氧-4-噁唑烷乙酸21.8克，产率：53.4%。

在100毫升三颈瓶中加入30毫升乙酸乙酯、4.31克(0.02摩尔)L-苯丙氨酸甲酯盐酸盐和1.64克(0.02摩尔)醋酸钠，室温机械搅拌15分钟，加入8.12克(0.02摩尔)上述的噁唑烷酮化合物，35℃恒温反应12小时，反应条件、操作按实施例三得N-甲酰基-天冬甜肽4.16克，产率：64.6%。

实施例十五

在2000毫升圆底烧瓶中加入134克(1摩尔)L-天冬氨酸，110毫升(2.55摩尔)85%甲酸和700毫升(7.4摩尔)乙酸酐，室温搅拌15分钟后，加入195毫升(2.0摩尔)三氯乙醛和800毫升乙酸，油浴加热，升温至75℃，反应15小时得淡黄色澄明液，50℃以下减压除去溶剂，得一棕色油状液，加入250毫升二氯甲烷溶解，-10℃冷冻析出晶体，过滤，石油醚洗涤，干燥得白色的2-三氯甲基-3-N-甲

酰基-5-氧-4- 噁唑烷乙酸210克，产率：72.3%。

在100毫升三颈瓶中加入上述的噁唑烷酮5.82克(0.02摩尔)和30毫升乙醚，机械搅拌下，室温滴加3.58克(0.02摩尔)L-苯丙氨酸甲酯，滴加完毕，40℃恒温反应12小时，反应条件、操作按实施例一得白色的N-甲酰基-天冬甜肽3.53克，产率：54.8%。

实施例十六

在100毫升三颈瓶中加入按实施例十五制备的 噁唑烷酮5.82克(0.02摩尔)和30毫升二氧六环，机械搅拌下，室温滴加 3.58克(0.02摩尔)L-苯丙氨酸甲酯，滴加完毕，40℃恒温反应10小时，反应条件、操作同实施例一 得N-甲酰基-天冬甜肽4.90克，产率：76.1%。

实施例十七

在100毫升三颈瓶中加入30毫升二氧六环、4.31克(0.02摩尔)L-苯丙氨酸甲酯盐酸盐和1.64克(0.02摩尔)醋酸钠，室温机械搅拌15分钟，加入5.82克(0.02摩尔)按实施例十五制备的噁唑烷酮化合物，60℃恒温反应8小时，反应条件、操作按实施例一得N-甲酰基-天冬甜肽5.22克，产率：81.1%。

实施例十八

在100毫升三颈瓶中加入按实施例十五制备的 噁唑烷酮 5.82克(0.02摩尔)和30毫升乙酸甲酯，机械搅拌下，室温滴加3.58克(0.02摩尔)L-苯丙氨酸甲酯，滴加完毕，30℃恒温反应15小时，

反应条件、操作按实施例一得N-甲酰基-天冬甜肽5.06克，产率：78.6%。

实施例十九

在100毫升三颈瓶中加入30毫升乙酸甲酯、4.31克(0.02摩尔)L-苯丙氨酸甲酯盐酸盐和1.64克(0.02摩尔)醋酸钠，室温机械搅拌15分钟，加入5.82克(0.02摩尔)按实施例十五制备的噁唑烷酮化合物，60℃恒温反应8小时，反应条件、操作按实施例一得N-甲酰基-天冬甜肽5.20克，产率：80.7%。

实施例二十

100毫升三颈瓶中加入40毫升乙酸丙酯、4.32克(0.02摩尔)L-苯丙氨酸甲酯盐酸盐和1.97克(0.024摩尔)醋酸钠，室温机械搅拌15分钟，加入5.82克(0.02摩尔)按实施例十五制备的噁唑烷酮化合物，40℃恒温反应12小时，反应条件、操作按实施例三得N-甲酰基-天冬甜肽5.34克，产率：82.9%。

实施例二十一

在100毫升三颈瓶中加入按实施例十五制备的 噁唑烷酮 8.12克(0.028摩尔)和30毫升乙酸丙酯，机械搅拌下，室温滴加3.58克(0.02摩尔)L-苯丙氨酸甲酯，滴加完毕，40℃恒温反应10小时，反应条件、操作按实施例三得N-甲酰基-天冬甜肽5.46克，产率：84.7%。

实施例二十二

100毫升三颈瓶中加入30毫升乙酸丙酯、4.31克(0.02摩尔)L-苯丙氨酸甲酯盐酸盐和1.64克(0.02摩尔)醋酸钠，室温机械搅拌15分钟，加入5.82克(0.02摩尔)按实施例十五制备的噁唑烷酮化合物，90℃恒温反应5小时，反应条件、操作按实施例三得N-甲酰基-天冬甜肽4.43克，产率：68.8%。